Smell Dysfunction: A Biomarker for COVID-19

Shima T. Moein, MD, PhD[1], Seyed M.R. Hashemian, MD, FCCM[2], Babak Mansourafshar, MD[2], Ali Khorram-Tousi, MD[1], Tabarsi, P., M.D.,[3] Richard L. Doty, PhD, FAAN[4*]

[1] School of Biological Sciences, Institute for Research in Fundamental Sciences, Tehran, Iran

[2] Chronic Respiratory Diseases Research Center, National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran

[3] Clinical Tuberculosis and Epidemiology Research Center, National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran

[4] Smell & Taste Center, Department of Otorhinolaryngology-Head and Neck Surgery, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

*corresponding author (doty@pennmedicine.upenn.edu)

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/alr.22587.

Disclosures: Dr. Doty is a consultant to Acorda Therapeutics, Eisai Co, Ltd, Merck Pharmaceuticals, the Michael J. Fox Foundation for Parkinson's Research, and Johnson & Johnson. He receives royalties from Cambridge University Press, Johns Hopkins University Press, and John Wiley & Sons, Inc. He is president of, and a major shareholder in, Sensonics International, a manufacturer and distributor of smell and taste tests, including the test used in this study. The other authors have nothing to disclose.

Abstract

Background: SARS-CoV-2, the virus that causes COVID-19 disease, is responsible for the largest pandemic since the 1918 H1N1 influenza outbreak. The symptoms presently recognized by the World Health Organization are cough, fever, tiredness, and difficulty breathing. Patient-reported smell and taste loss has been associated with COVID-19 infection, yet no empirical olfactory testing on a cohort of COVID-19 patients has been performed.

Methods: The University of Pennsylvania Smell Identification Test (UPSIT), a well-validated 40-odorant test, was administered to 60 confirmed COVID-19 inpatients and 60 age- and sex-matched controls to assess the magnitude and frequency of their olfactory dysfunction. A mixed effects analysis of variance determined whether meaningful differences in test scores existed between the two groups and if the test scores were differentially influenced by sex.

Results: Fifty-nine (98%) of the 60 patients exhibited some smell dysfunction [mean (95% CI) UPSIT score: 20.98 (19.47,22.48); controls: 34.10 (33.31,34.88); $p<0.0001$]. Thirty-five of the 60 patients (58%) were either anosmic (15/60; 25%) or severely microsmic (20/60; 33%); 16 exhibited moderate microsmia (16/60; 27%), 8 mild microsmia (8/60; 13%), and one normosmia (1/60; 2%). Deficits were evident

for all 40 UPSIT odorants. No meaningful relationships between the test scores and sex, disease severity, or comorbidities were found.

Conclusions: Quantitative smell testing demonstrates that decreased smell function, but not always anosmia, is a major marker for SARS-CoV-2 infection and suggests the possibility that smell testing may help, in some cases, to identify COVID-19 patients in need of early treatment or quarantine.

Introduction

Recently there have been numerous reports in the media that anosmia occurs in persons who have contracted coronavirus disease 2019 (COVID-19) by exposure to the SARS-COV-02 virus. These include one published single case report,[1] and self-report surveys from Germany,[2] Great Britain,[3] Iran,[4] Italy,[5] and the United States,[6] with smell loss reports ranging from 34% to 68% of COVID-19 positive patients. Otorhinolaryngology authorities have warned that loss of smell and taste, in combination with other symptoms, appears to be a strong predictor of COVID-19 infection.[7,8]

To date, validated quantitative olfactory testing has not been performed in a cohort of COVID-19 patients to verify or determine the true magnitude of their deficits and whether less-than-total loss occurs in some patients. Moreover, the proportion of COVID-19 patients exhibiting true olfactory disturbances is unknown. Most studies suggest that, in general, a significant number of persons with smell loss are unaware of their deficit until formal testing[9] and that self-reports of both smell and taste abilities correlate poorly with the results of quantitative smell and taste tests.[10,11]

In this case-control study, we administered the Persian version of the 40-item University of Pennsylvania Smell Identification Test (UPSIT)[12] to 60 confirmed

COVID-19 patients and 60 age- and sex-matched controls to assess the presence, magnitude, and frequency of their olfactory dysfunction. We determined whether the smell loss was related to the sex of the subjects and inquired, for those patients who were aware of their dysfunction before testing, when they first noticed their chemosensory disorder.

Methods:

Subjects

The age, sex, comorbidities, smoking status, and complaints of chemosensory dysfunction of the 120 study participants are presented in Table 1. The 60 SARS-COV-02 positive subjects had been admitted with the symptoms of COVID-19 to the Masih Daneshvari Hospital, Tehran, Iran, between March 21, 2020 and March 23, 2020 or March 31, 2020 and April 5, 2020. At the time of the olfactory testing, all were inpatients in the recovery period of the disease and were ready to be discharged within 4 days. The study was explained in detail to 68 such patents, of which 8 declined to participate (i.e., the participation rate was 88%).

The control subjects were from a database of 141 subjects collected in Iran for an earlier study. They were tested in the olfactory laboratory of the Institute for Research in Fundamental Sciences, Tehran, Iran, and comprised a convenience sample obtained from email lists, flyers, and word of mouth. None had influenza or common cold symptoms at the time of testing. The recruitment period for this database (August 8, 2019 to February 13, 2020) preceded the first reported confirmed cases of COVID-19 in Iran (February 19, 2020). A control subject was individually matched as closely as possible to each COVID-19 patient. Exact age matches were possible for 34 subjects, 1-year differences for 22 subjects, and 2-year differences

for 4 subjects. In cases where more than one match was possible, the first match in the database sequence was used.

Informed written consent was obtained from each patient and control, and the study protocol was approved by the local ethics committee and the Iranian Ministry of Health (license number IR.SBMU.NRITLD.REC.1399.013). All testing was performed with the highest regard for examiner safety with appropriate personal protective equipment.

Diagnosis and Clinical Severity Classification of COVID-19 Patients

COVID-19 diagnosis was based on the COVID-19 detection protocol of Masih Daneshvari Hospital. All of the patients underwent 16-slice chest CT imaging (Scope Power Siemens CT Scan, Munich, Germany) and had positive chest CT findings.[13] Subsequently, the diagnosis of COVID-19 disease was confirmed by quantitative detection of SARS-CoV-2 RNA using the real-time reverse transcription polymerase chain reaction (rRT-PCR) in respiratory specimens.[14] The RT-PCR assays were performed using Sansure Biotech's 2019-nCoV 30-Minute Nucleic Acid Reagent Kits (Sansure Biotech, Inc., Development Zone Changsha, China). The respiratory specimens were collected from the patients' nasopharyngeal wash/aspirate or nasal aspirate.

COVID-19 clinical severity was classified as mild, moderate, or severe according to Massachusetts General Hospital COVID-19 treatment guidance for treatment algorithm.[15] Mild clinical COVID-19 presentation was defined as having SpO2 > 90% along with or without risk factors. Moderate clinical COVID-19 presentation was considered for patients who had at least one epidemiological risk factor along with a risk factor in vital signs or laboratory findings at the admission point of time. Patients in the intensive care unit (ICU) or with progressive disease were classified as having

severe clinical presentation of COVID-19. Epidemiological risk factors included age > 55 years or pre-existing pulmonary disease, chronic kidney disease, diabetes with A1c > 7.6%, history of hypertension or cardiovascular disease or transplant or immunosuppression or HIV. Risk factors of vital signs comprised respiratory rate > 24 breaths/min, heart rate > 125 beats/min and SpO2 < 90% on ambient air. In lab findings, D-dimer > 1000 ng/mL, CPK > twice upper limit of normal, CRP > 100, LDH > 245 U/L, elevated troponin, admission absolute lymphocyte count < 0.8 and ferritin > 300 ug/L. For COVID-19 patients with mild disease with SpO2>90%, supportive care was provided and hydroxychloroquine administration was started (200 mg BID x 2 doses, then 100 mg BID for 5 days). For the patients with moderate to severe COVID-19 presentations, lopinavir/ritonavir 200/50 mg BID for up to 10 days) was prescribed. In patients with progressive COVID-19 disease admitted to the ICU, intravenous immunoglobulin (IVIG) at standard dose of 0.5 g/kg/day daily for 5 days was administered.[16]

Olfactory Testing

The Persian version of the 40-odorant University of Pennsylvania Smell Identification Test (UPSIT) was administered in this study (Sensonics International, Haddon Hts., NJ, USA). The UPSIT is a well-validated and reliable (test-retest r = 0.94) test that employs microencapsulated “scratch and sniff” odorants.[11,12,17,18] It provides an index of absolute dysfunction (i.e., anosmia, severe microsmia, moderate microsmia, mild microsmia, normosmia, malingering), as well as relative dysfunction based upon age- and gender-adjusted normative percentile ranks. The total number of odorant stimuli out of 40 that is correctly identified serves as the test measure. Scores on this test correlate well with other types of olfactory tests, including threshold tests.[19] Although the UPSIT is designed to be self-administered, to be certain that the

COVID-19 patients correctly performed the test during the limited clinical time window, the testing was assisted by a trained examiner.

Statistical Analyses

Statistical analyses were performed using either SYSTAT 13[20] or MATLAB 2019b (The MathWorks, Inc., Natick, MA, USA). A subject group by gender mixed factor analysis of variance (ANOVA) was used to determine whether the UPSIT scores differed significantly between the patient and control groups and whether gender influenced the test scores. Standard ANOVAs were used to compare other means. Differences in frequencies were assessed using the Fisher's Exact Probability Test.

Results

The COVID-19 patients' non-mutually exclusive presenting symptoms were fever (n = 46, 77%), cough (n = 35, 58%), shortness of breath (n = 31, 52%), headache (n = 22, 37%), myalgia (n = 5, 8%), sweating (n = 2, 3%), shivering (n = 2, 3%), anorexia (n = 2, 3%), stomach ache (n = 1, 2%), and tinnitus (n = 1, 2%). The UPSIT testing revealed that, relative to controls and published normative data, the COVID-19 patients exhibited marked olfactory dysfunction. Thus, as illustrated in Figure 1, the mean (95% CI) UPSIT score for the COVID-19 patients was 20.98 (19.47, 22.48), reflecting severe microsmia,[21] whereas the mean UPSIT score (95% CI) for the age- and sex-matched controls fell within the normal range [34.10 (33.31, 34.88); ANOVA group main effect $F(1,58) = 232.99$, $p < 0.0001$, $\eta^2 = 0.80$]. The COVID-19 deficit was not specific to any one UPSIT odorant, being evident for all 40 stimuli (Figure 2).

Importantly, all but one of the 60 patients with COVID-19 had some degree of measured olfactory dysfunction (98%). Thirty-five of the 60 patients (58%) were either anosmic (15/60; 25%) or severely microsmic (20/60; 33%); 16/60 (27%) exhibit-

ed moderate microsmia, 8/60 (13%) mild microsmia, and 1/60 (2%) normosmia according to UPSIT norms (Table 2).[21] This contrasts markedly from the controls, of which 49/60 (82%) were normal with the remaining 11/60 (18%) having only mild borderline dysfunction. Relative to the normal controls, the 11 controls with mild borderline dysfunction tended to be disproportionately men [10/11 (91%) vs. 30/49 (61%); p = 0.08] of older age [respective mean ages (95% CIs) = 51.18 (42.63, 59.73) & 45.51 (42.11, 48.90); p = 0.18]. Even though there was a tendency for women, overall, to outperform men on the UPSIT [respective mean (95% CI) UPSIT scores: 22.55 (20,13, 24.97) & 20.20 (18.27, 22.13) [F (1,58) = 3.82, p = 0.055, η^2 = 0.06], this was unrelated to COVID-19 [sex by group interaction F (1,58) = 0.396, p = 0.53].

Thirty-five percent (21/60) of the COVID-19 patients reported a loss in either smell or taste function, with 12% (7/60) reporting smell loss only, 7% (4/60) taste loss only, and 17% (10/60) both taste and smell loss. There was no significant difference between UPSIT scores of patients who were aware or unaware of their chemosensory loss (p = 0.28). All 21 reported that the onset of the olfactory dysfunction occurred at the same time or immediately after the onset of their other COVID-19 symptoms. None reported recognizing any smell or taste deficits prior to their other COVID-19 symptoms, namely fever, cough, or shortness of breath. In the healthy control group, none of the participants reported any smell or taste problems.

As shown in Table 1, significantly fewer smokers were present in the COVID-19 group than in the control group [2/60 vs. 11/60; p = 0.016]. Eight patients with diabetes were present in the COVID-19 group, unlike the control group [8/60 vs. 0/60; p = 0.007]. However, the respective mean (95% CI) UPSIT scores for COVID-19 patients with and without diabetes did not differ [21.38 (18.18, 24.56) vs. 20.92 (19.32,

22.62), respectively; F (2,57) = 1.43, p = 0.24, η^2 = 0.05]. No association of UPSIT scores with disease severity, as per the Massachusetts General Hospital COVID-19 treatment guidance algorithm, was apparent [Table 3; F (2,57) = 1.45, p = 0.24, η^2 = 0.05].

Discussion

This study quantitatively evaluated olfaction in a sizable cohort of patients diagnosed with the SARS-CoV-2 virus infection. By employing a well-validated 40-item smell test, COVID-19 patients were able to be classified into distinct categories of olfactory dysfunction, with 50 of 60 (83%) exhibiting either anosmia or severe microsmia. In the present study, only 35% of the patients were aware of their olfactory deficit before testing, a percentage nearer to that of 34% reported in an interview with COVID-19 inpatients in Italy,[5] but lower than those reported in two online surveys (59%[3] and 68%[6]). This difference between self-report rate and quantified smell assessment conceivably reflects either a disproportionate sampling of hospital admitted cases or the well-documented underestimation of self-reported smell and taste dysfunction present for the general population[9,10] and for such diseases as Alzheimer's[11] and Parkinson's disease.[22,23] In general, smell loss is most noticeable when marked loss, such as anosmia, is present.[11,22] It should be pointed out that the present study's sample resembles the demographic and clinical characteristics of COVID-19 patients reported in a compilation of 43 studies involving 3600 patients,[24] implying it is likely representative of COVID-19 patients in general.

The basis for the smell loss due to SARS-CoV-2 is not entirely clear, although it is well established that viruses and other xenobiotics can damage the olfactory neuroepithelium. Indeed, acute viral upper respiratory viral infections that damage this epithelium are the major cause of chronic olfactory dysfunction and numerous

viruses are known to enter the brain through cellular and pericellular transport via this epithelium.[25] In North America, the peak period of non-influenza-related smell loss, including that possibly due to coronaviruses, occurs during the months of April, May, and June, whereas for influenza-related viral loss peaks in December, January and February.[26] Currently, the prevalence of COVID-19 in North America seems to follow a similar function to that observed for olfactory deficits due to other viruses, including other coronaviruses. What seems unique, however, is that nearly every-one who contacts COVID-19 appears to exhibit measurable loss of smell seemingly independent of severe nasal congestion or inflammation.

Although SARS-CoV-2 has the ability to enter epithelial cells by directly bind-ing to the angiotensin converting enzyme 2 (ACE2) protein on the cell surface,[27] ol-factory receptor cells do not express ACE2, as well as another gene involved in CoV-2 entry (TMPRSS2), unlike epithelial sustentacular and stem cells.[28] Thus, damage to the olfactory receptors may be mediated indirectly through SARS-CoV-2 uptake into other cells critical for sustaining the olfactory receptor cell population. For example, olfactory ensheathing glial cells that surround the olfactory receptor cell axons and form the olfactory fila are one candidate by which ACE2-independent vi-rus transfer can occur into olfactory receptor neurons by way of exosomes. A possi-ble scenario suggests that at this point olfactory receptor neurons may initiate a rapid immune response in the host with the manifestation of olfactory dysfunction.[29] That being said, the olfactory neuroepithelium has considerable propensity for regenera-tion if the stem cell layer is not markedly damaged[30-32] – regeneration that is likely related to spontaneous improvement in olfactory function over time.[33]

It is of interest that significantly fewer smokers were found in our COVID-19 cohort than in the control cohort. Our findings correspond with studies that report

current smokers as rare as 1.4% and 1.3% in Chinese[34] and US[35] COVID-19 patient populations, respectively. A recent study reported that smoking upregulated the expression of ACE-2 in the airways, potentially predisposing individuals to increased risk of coronavirus infection but, paradoxically, protecting the host against acute lung injury.[36] Interestingly, non-smokers appear to be much more susceptible than smokers to olfactory dysfunction from industrial exposures to acrylate and methacrylate [37] and smoking appears to protect, to some degree, the olfactory loss of Parkinson's disease.[38] Future research is needed to determine to what degree the reported low frequency of smokers in COVID-19 populations is impacted by selection bias (e.g., more smokers may have died before reaching the hospital) and reverse causation (i.e., cessation of smoking in patients with severe symptoms prior to entering the hospital, thereby being counted as non-smokers). The latter is unlikely in our study, however, since each patient was specifically asked whether they currently smoke or had smoked in the past.

The complaint of taste loss by a small number of our COVID-19 patients most likely reflects, to a significant degree, damage to the olfactory system, rather than damage to the taste buds or taste afferents, per se. Thus, the vast majority of individuals who clinically present with complaints of taste loss actually exhibit smell dysfunction, including those with a viral etiology.[39] Taste bud-mediated sensations are largely limited to the basic taste qualities of sweet, sour, bitter, salty, and umami. With the exception of such sensations, all "tastes" are flavor sensations from olfactory receptor stimulation by volatiles entering from the nasopharynx during deglutition.[40] This tendency for many persons with smell loss to misconstrue their problem as taste loss [39] must be considered in studies relying only on self-report. Future research employing quantitative taste tests is clearly needed to definitively

establish whether SARS-CoV-2 also can damage taste afferents or, in rare cases, more central taste-related brain regions.

More men than women were present in our sample, in accord with the reported demographic and clinical characteristics of COVID-19 patients.[24] However, the magnitude of olfactory dysfunction, as measured by the UPSIT, was essentially the same in both sexes. This implies that there is little or no protection from being a female in terms of the degree to which SARS-CoV-2 damages the olfactory system, in accord with some other studies of post-viral olfactory deficits.[41] If this observation is confirmed with larger samples, it would appear that the olfactory dysfunction of COVID-19 differs from that of Alzheimer's disease (AD) and Parkinson's disease (PD), where women significantly outperform men.[11,22,38]

It is important to note that the COVID-19 positive patients evaluated in this study had severe enough symptoms to be admitted to hospital. It is unknown whether less severe cases also exhibit the same degree of smell dysfunction as documented in this study, although within our hospitalized cohort no relationship was evident between the olfactory test scores and disease severity. This is similar to what is seen in the smell loss of PD, where no clear association is present between the magnitude of the classic motor signs and the amount of olfactory dysfunction.[22]

Even though the COVID-19 patients in this study were undergoing drug treatments for their disease, it is unlikely that the involved drugs were a meaningful cause of their olfactory dysfunction. Despite the fact that a significant number of medications are reported to have taste side effects,[42] alterations in smell function are relatively rare and have not been associated with hydroxychloroquine, Lipinavir-Ritonavir, or IVIG. Since the same degree of smell function was evident among pa-

tients with COVID-19 taking each of these medications, it is improbable that any one medication would have produced the smell deficits observed in this study.

While RT-PCR was by far the frontline response to the SARS-CoV-2 outbreak, the accuracy and conditions under which the results of RT-PCR were achieved must be kept in context, since a false negative rate of at least 15% has been reported.[43-45] The present findings, along with the wealth of anecdotal data, suggest that quantitative testing of the sense of smell might serve as a rapid and inexpensive alternative diagnostic means to screen for COVID-19 in large numbers of individuals. Indeed, the sensitivity and specificity of olfactory tests for COVID-19 positive patients under the age of 65 would seem to be quite strong, since age-related changes in smell function occur mainly after the age of 65.[17]

The present study has both strengths and weaknesses. Among its strengths are (a) the use of a sensitivity test of olfactory function that allows for determining different degrees of olfactory function, (b) testing of well-validated COVID-19 patients whose clinical severity was well documented, and (c) the use of controls matched closely to those of the patients on the basis of age and sex who were sampled outside of the period in which COVID-19 was first identified in Iran. Its major limitation is the sampling of the study population at only one point in time relative to the onset of COVID-19 symptoms. Future studies are needed to establish (a) the exact time of onset of smell symptoms, (b) whether the olfactory dysfunction is transient, long-lasting, or permanent, (c) whether such symptoms are evident in those who fail to develop other COVID-19 symptoms, and (d) whether the deficits follow seasonal patterns such as those noted for other virus-related cases of smell dysfunction.[56] Information as to permanency is of considerable significance, since loss of the ability to smell significantly impacts quality of life, the flavor of foods and beverages, and safe-

ty from spoiled food, fire, and leaking natural gas. Importantly, smell loss can be a harbinger of a number of neurological diseases, most notably AD and PD – diseases which, in some cases, have been associated with a number of viruses.[46,47] While the reasons are poorly understood, older persons with smell loss are three times more likely to die over the course of an ensuring half-decade than older persons with a normal sense of smell. [48,49]

In conclusion, the present study provides a quantitative assessment of the olfactory function of a cohort of patients with COVID-19. Its findings strongly suggest that some degree of loss of smell function is present in nearly all COVID-19 patients near the end of their acute recovery period. However, anosmia, per se, was present in only about a quarter of COVID-19 positive patients in our sample, with about a third evidencing severe microsmia. In light of the current findings and pandemic environment, and the widespread anecdotal evidence of smell dysfunction in COVID-19, it does not seem unreasonable that testing the olfaction of persons who may be at risk or have subtle COVID-19 signs, such as low grade fevers, may aid in identifying COVID-19 patients who are in need of early treatment or quarantine.

Acknowledgments

We would like to thank Mr. Iraj Fotouhi for his invaluable help in assisting patients during smell testing, Ms. Crystal Wylie for comments on a draft of the paper, and Dr. Kambiz Pourrezaei for insightful discussions of the research.

Table 1. Patient and control subject demographics. Significant p differences indicated in bold.

		COVID-19 patients	Controls	Fisher Exact Probability Test P
Sample Size		**60**	**60**	
Mean Age (SD)		**46.55 (12.17)**	**46.55 (12.07)**	
Gender		**40 M & 20 F**	**40 M & 20 F**	
Current/Never Smoker		2/58	11/49	**0.016**
Taste/Smell Complaints		21	0	**0.001**
Comorbidities	Asthma	3	0	0.244
	Atherosclerosis	0	2	0.496
	Autoimmune disease	4*	0	0.119
	Carcinoma	2**	0	0.496
	Congenital melonytic nevi	1	0	1.000
	Diabetes	8***	0	**0.007**
	Haemophilia	0	1	1.000
	Hepatic failure	0	1	1.000
	Hyperlipidemia	1	1	1.000
	Hypertension	6***	5	1.000
	Hypothyroidism	4***	2	0.679
	Migraine	0	1	1.000
	Osteoporosis	0	1	1.000
	Sinusitis	2	0	0.496

*Autoimmune disease included Behcet's disease in combination with Crohn's disease (n = 1), multiple sclerosis (n=2), and rheumatoid arthritis (n = 1). ** Prostate and cervical cancers; ***Although, in rare cases, changes in dosage and medications may have occurred during the course of inpatient treatments, most patients remained on their pre-admission medications.

Table 2. Classification of olfactory function of the UPSIT scores of COVID-19 patients and matched controls.

UPSIT Function Category	Number of COVID-19 Patients (Percent)	Number of Controls (Percent)	UPSIT Score Range
Normosmia	1 (2%)	49 (82%)	31-40
Mild Microsmia	8 (13%)	11 (18%)	28-30
Moderate Microsmia	16 (27%)	0	24-27
Severe Microsmia	20 (33%)	0	17-23
Anosmia	15 (25%)	0	6-16
Probable Malingering	0	0	0-5

Table 3. Relationship between COVID-19 clinical disease severity and mean (95% CI) scores on the University of Pennsylvania Smell Identification Test (UPSIT).

COVID-19 Disease Severity	Frequency (Percent)	Mean (95%CI) UPSIT Score
Mild	25 (42%)	22.04 (20.11, 24.72)
Moderate	29 (48%)	19.69 (17.24, 21.99)
Severe	6 (10%)	22.83 (17.65, 25.77)

References

1. Eliezer M, Hautefort C, Hamel AL, et al. Sudden and Complete Olfactory Loss Function as a Possible Symptom of COVID-19. *JAMA Otolaryngol Head Neck Surg* 2020. Apr 8. doi: 10.1001/jamaoto.2020.0832. [Epub ahead of print]

2. Luers JC, Klussmann JP, Guntinas-Lichius O. [The Covid-19 pandemic and otolaryngology: What it comes down to?]. *Laryngorhinootologie* 2020 Mar 26. doi: 10.1055/a-1095-2344. [Epub ahead of print]

3. Menni C VA, Freydin MB, Ganesh S, El-Sayed Moustafa J, Visconti A, et al. Loss of smell and taste in combination with other symptoms is a strong predictor of COVID-19 infection. *medRxiv 2020:2020032320041889* 2020.

4. Bagheri SHR AA, Farhadi M, Shamshiri AR, Kabir A, Kamrava SK, et al. . Coincidence of COVID-19 epidemic and olfactory dysfunction outbreak. . *medRxiv 2020:2020032320041889* 2020.

5. Giacomelli A, Pezzati L, Conti F, et al. Self-reported olfactory and taste disorders in SARS-CoV-2 patients: a cross-sectional study. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2020.

6. Yan CH, Faraji, M., Prajapati, D.P., Boone, C.E. Association of chemosensory dysfunction and Covid-19 in patients presenting with influenza-like symptoms. *Int Forum Allergy Rhinol* 2020 https://doi.org/10.1002/air.22579.

7. Hyposmia and Anosmia. 2020. https://www.enthealth.org/conditions/hyposmia-and-anosmia/.

8. Hopkins C KN. Loss of sense of smell as marker of COVID-19 infection 2020. https://www.entuk.org/sites/default/files/files/Loss%20of%20sense%20of%20smell%20as%20marker%20of%20COVID.pdf.

9. Wehling E, Nordin S, Espeseth T, Reinvang I, Lundervold AJ. Unawareness of olfactory dysfunction and its association with cognitive functioning in middle aged and old adults. *Arch Clin Neuropsychol* 2011; **26**(3): 260-9.

10. Soter A, Kim J, Jackman A, Tourbier I, Kaul A, Doty RL. Accuracy of self-report in detecting taste dysfunction. *Laryngoscope* 2008; **118**(4): 611-7.

11. Doty RL, Reyes PF, Gregor T. Presence of both odor identification and detection deficits in Alzheimer's disease. *Brain Resh Bull* 1987; **18**(5): 597-600.

12. Doty RL, Shaman P, Dann M. Development of the University of Pennsylvania Smell Identification Test: a standardized microencapsulated test of olfactory function. *Physiol Behav* 1984; **32**: 489-502.

13. Chung M, Bernheim A, Mei X, et al. CT Imaging Features of 2019 Novel Coronavirus (2019-nCoV). *Radiology* 2020; **295**(1): 202-7.

14. Zou L, Ruan F, Huang M, et al. SARS-CoV-2 Viral Load in Upper Respiratory Specimens of Infected Patients. *N Engl J Med* 2020; **382**(12): 1177-9.

15. Massachusetts General Hosital COVID-19 Treatment Guidance. https://www.massgeneral.org/assets/MGH/pdf/news/coronavirus/covid-19_domID_treatmentGuide.pdf 2020 (Accessed March 21, 2020)

16. Jamaati H DF, Tabarsi P, Marjani M, Saffaei A, Hashemian SM. A Fourteen-day Experience with Coronavirus Disease 2019 (COVID-19) Induced Acute Respiratory Distress Syndrome (ARDS): An Iranian Treatment Protocol. *Iran J Pharm Res* 2020 in press.

17. Doty RL, Shaman P, Applebaum SL, Giberson R, Siksorski L, Rosenberg L. Smell identification ability: changes with age. *Science* 1984; **226**: 1441-3.

18. Doty RL, Frye RE, Agrawal U. Internal consistency reliability of the fractionated and whole University of Pennsylvania Smell Identification Test. *Percept Psychophys* 1989; **45**(5): 381-4.

19. Doty RL, Wylie C, Potter M, Beston R, Cope B, Majam K. Clinical validation of the olfactory detection threshold module of the Snap & Sniff(R) olfactory test system. *Int Forum Allergy Rhinol* 2019; **9**(9): 986-92.

20. Wilkinson L. SYSTAT: The System for Statistics. Evanston, II:: SYSTAT, Inc.; 1990.

21. Doty RL. The Smell Identification Test™ Administration Manual -- 3rd Edition. Haddon Hts., NJ: Sensonics, Inc.; 1995.

22. Doty RL, Deems DA, Stellar S. Olfactory dysfunction in parkinsonism: a general deficit unrelated to neurologic signs, disease stage, or disease duration. *Neurology* 1988; **38**(8): 1237-44.

23. Doty RL, Perl DP, Steele JC, et al. Odor identification deficit of the parkinsonism-dementia complex of Guam: Equivalence to that of Alzheimer's and idiopathic Parkinson's disease. *Neurology* 1991; **41**(5 Suppl 2): 77-80.

24. Fu L, Wang B, Yuan T, et al. Clinical characteristics of coronavirus disease 2019 (COVID-19) in China: a systematic review and meta-analysis. *J Infect* 2020 Apr 10. pii: S0163-4453(20)30170-5. doi: 10.1016/j.jinf.**2020**.03.041. [Epub ahead of print]

25. Doty RL. The olfactory vector hypothesis of neurodegenerative disease: is it viable? *Ann Neurol* 2008; **63**(1): 7-15.

26. Potter MRC, J.; Lobban, N-S.; Doty,R.L. Olfactory dysfunction from acute upper respiratory infections: Relationship to season of onset. *Int Forum Allergy Rhinol.* 2020 Apr 13. doi: 10.1002/alr.22551. [Epub ahead of print]

27. Qi F, Qian S, Zhang S, Zhang Z. Single cell RNA sequencing of 13 human tissues identify cell types and receptors of human coronaviruses. *Biochem Biophys Res Commun* 2020. Mar 18. pii: S0006-291X(20)30523-4. doi: 10.1016/j.bbrc.2020.03.044. [Epub ahead of print]

28. Brann DH, Tsukahara, T., Weinreb, C., Logan, D.W., Datta, S.R. Non-neural expression of SARS-ClV-2 entry genes in the olfactory epithelium suggests mechanisms underlying anosmia in COVD-19 patients. *BioRxiv 2020 doi: https://doi.org/10.1101/2020.03.25.009084*

29. Butowt R, Bilinska K. SARS-CoV-2: Olfaction, Brain Infection, and the Urgent Need for Clinical Samples Allowing Earlier Virus Detection. *ACS Chem Neurosci* 2020 Apr 13. doi: 10.1021/acschemneuro.0c00172. [Epub ahead of print]

30. Chang SY, Glezer I. The balance between efficient anti-inflammatory treatment and neuronal regeneration in the olfactory epithelium. *Neural Regen Res* 2018; **13**(10): 1711-4.

31. Choi R, Goldstein BJ. Olfactory epithelium: Cells, clinical disorders, and insights from an adult stem cell niche. *Laryngoscope Investig Otolaryngol* 2018; **3**(1): 35-42.

32. Joiner AM, Green WW, McIntyre JC, Allen BL, Schwob JE, Martens JR. Primary Cilia on Horizontal Basal Cells Regulate Regeneration of the Olfactory Epithelium. *J Neurosci* 2015; **35**(40): 13761-72.

33. London B, Nabet B, Fisher AR, White B, Sammel MD, Doty RL. Predictors of prognosis in patients with olfactory disturbance. *Ann Neurol* 2008; **63**(2): 159-66.

34. Zhang JJ, Dong X, Cao YY, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. *Allergy* 2020. Feb 19. doi: 10.1111/all.14238. [Epub ahead of print]

35. DHHS. Preliminary Estimates of the Prevalence of Selected Underlying Health Conditions Among Patients with Coronavirus 2910 j-- United States, February 12l-March 28, 2020. *MMWR Morb Mortal Wkly Rep* 2020; **69**: 382-6.

36. Leung JM, Yang CX, Tam A, et al. ACE-2 Expression in the Small Airway Epithelia of Smokers and COPD Patients: Implications for COVID-19. *Eur Respir J.* 2020 Apr 8. pii: 2000688. doi: 10.1183/13993003.00688-2020. [Epub ahead of print]

37. Schwartz BS, Doty RL, Monroe C, Frye R, Barker S. Olfactory function in chemical workers exposed to acrylate and methacrylate vapors. *Amer J Pub Health* 1989; **79**(5): 613-8.

38. Sharer JD, Leon-Sarmiento FE, Morley JF, Weintraub D, Doty RL. Olfactory dysfunction in Parkinson's disease: Positive effect of cigarette smoking. *Mov Disord* 2015; **30**(6): 859-62.

39. Deems DA, Doty RL, Settle RG, et al. Smell and taste disorders, a study of 750 patients from the University of Pennsylvania Smell and Taste Center. *Arch Otolaryngol Head Neck Surg* 1991; **117**(5): 519-28.

40. Burdach KJ, Doty RL. The effects of mouth movements, swallowing, and spitting on retronasal odor perception. *Physiol Behav* 1987; **41**(4): 353-6.

41. Tian J, Wei YX, Li L, Sun ZF, Wang BQ. [Analysis of clinical characteristics of 141 patients with postviral olfactory dysfunction]. *Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi* 2017; **31**(10): 749-52.

42. Schiffman SS. Influence of medications on taste and smell. *World J Otorhinolaryngol Head Neck Surg* 2018; **4**(1): 84-91.

43. Li D, Wang D, Dong J, et al. False-Negative Results of Real-Time Reverse-Transcriptase Polymerase Chain Reaction for Severe Acute Respiratory Syndrome Coronavirus 2: Role of Deep-Learning-Based CT Diagnosis and Insights from Two Cases. *Korean J Radiol* 2020; **21**(4): 505-8.

44. Ai J-W ZH-C, Xu T, Wu J, Zhu M, Yu Y-Q et al. Optimizing diagnostic strategy for novel coronavirus pneumonia, a multi-center study in Eastern China. . *medRxiv* 2020. medRxiv doi: https://doi.org/10.1101/2020.02.13.20022673

45. Liang Y LJ, Zhou Q, Li X, Lin F, Deng Z, et al. Prevalence and clinical features of 2019 novel coronavirus disease (COVID-19) in the Fever Clinic of a teaching hospital in Beijing: a single-center, retrospective study. *medRxiv* 2020. https://doi.org/10.1101/2020.02.25.2002776

46. Balin BJ, Hudson AP. Herpes viruses and Alzheimer's disease: new evidence in the debate. *Lancet Neurol* 2018; **17**(10): 839-41.

47. Olsen LK, Cairns AG, Aden J, et al. Viral mimetic priming enhances alpha-synuclein-induced degeneration: Implications for Parkinson's disease. *Brain Behav Immun* 2019; **80**: 525-35.

48. Pinto JM, Wroblewski KE, Kern DW, Schumm LP, McClintock MK. Olfactory dysfunction predicts 5-year mortality in older adults. *PLoS One* 2014; **9**(10): e107541.

49. Devanand DP, Lee S, Manly J, et al. Olfactory deficits predict cognitive decline and Alzheimer dementia in an urban community. Ann *Neurol* 2015; **84**(2): 182-9.

Figure 1. University of Pennsylvania Smell Identification Test (UPSIT) scores of the COVID-19 patients compared to those of healthy controls. The distribution of the participants' scores in each group is depicted in violin plot. The white circles indicate the median of the score for each group.

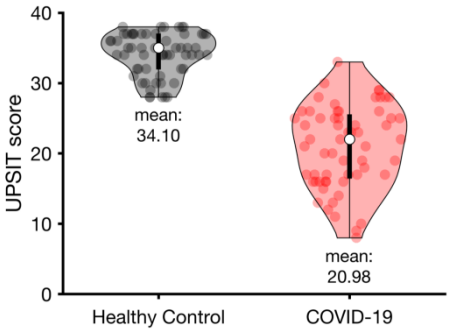

Figure 2. Performance on individual University of Pennsylvania Smell Identification Test (UPSIT) odorants
for the COVID-19 patients and matched healthy controls. Note that dysfunction was evident for all 40 UPSIT odorants. Performance for each group is calculated as the percent of individuals having correctly identified
the odorant.